

**APPENDIX I**

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# PHYSICIANS' DESK REFERENCE®

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the legs (as measured by the I-125 angiography) and of clinical pulmonary embolism. The recommended dosage is 5,000 units of heparin sodium given every 8 to 12 hours or until the patient is fully anticoagulated. The heparin is given by intravenous injection with a fine (25- to 30-gauge) needle, above the iliac crest or above the knee, in a 25- to 30-gauge needle. A concentrated solution is recommended. Such prophylaxis is recommended for patients over the age of 40 who are undergoing surgery. Patients with bleeding disorders or spinal-cord surgery, spinal anesthesia, or potentially sanguineous operations from this treatment, as should patients on anticoagulants or platelet-active drugs. The possibility of increased bleeding postoperatively should be borne in mind. Discontinuation of heparin and protamine sulfate are advisable. If clinical bleeding develops despite low-dose heparin, additional doses of anticoagulants should be administered. Prior to initiating heparin therapy, the probability of bleeding should be ruled out by a thorough history and performing coagulation tests. Appropriate coagulation tests should be performed prior to surgery. Coagulation should be normal or only slightly elevated at the time of surgery. Follow equipment manufacturers' instructions carefully.

**Heparin (Heparin Lock) Sets**—To prevent heparin lock set following its proper use, solution (see USP monograph for Heparin, USP) should be injected via a quantity sufficient to fill the entire set. The solution should be replaced each time the aspirate before administering any medication to confirm the patency and location of the catheter tip. If the drug to be administered with heparin, the entire heparin lock set should be flushed with sterile water or normal saline. The medication is administered; following this, the dilute heparin solution may be administered. The set manufacturer's instructions should be followed concerning the heparin lock set.

**Small doses of heparin**—Small doses of heparin (10 to 20 units) should be administered prior to partial thromboplastin time (PTT) should be obtained prior to surgery.

**Humatrope (Somatropin, rDNA Origin, for Injection)** is a recombinant DNA origin. Humatrope contains 5 mg somatropin (500 IU) or 225 nanomoles; 25 mg mannitol; 100 mg dibasic sodium phosphate; and 10 mg sodium hydroxide may have been

added at the time of manufacture to adjust the pH. This product is oxygen sensitive. Each vial is supplied in a combination package with an accompanying 5-mL vial of diluting solution. The diluent contains water for injection with 0.3% m-cresol as a preservative and 1.7% glycerin added at the time of manufacture.

Humatrope is a highly purified preparation. The 1.7% glycerin content makes the reconstituted product nearly isotonic at a concentration of 2 mg of Humatrope/mL diluent. Reconstituted solutions have a pH of approximately 7.5.

#### CLINICAL PHARMACOLOGY

**Linear Growth**—Humatrope® (Somatropin, rDNA Origin, for Injection) stimulates linear growth in children who lack adequate normal endogenous growth hormone. In vitro, pre-clinical, and clinical testing have demonstrated that Humatrope is therapeutically equivalent to human growth hormone of pituitary origin and achieves equivalent pharmacokinetic profiles in normal adults. Treatment of growth-hormone-deficient children with Humatrope produces increased growth rate and IGF-1 (Insulin-like Growth Factor/Somatomedin-C) concentrations similar to those seen after therapy with human growth hormone of pituitary origin. In addition, the following actions have been demonstrated for Humatrope and/or human growth hormone of pituitary origin.

**A. Tissue Growth**—1. **Skeletal Growth**: Humatrope stimulates skeletal growth in patients with growth hormone deficiency. The measurable increase in body length after administration of either Humatrope or human growth hormone of pituitary origin results from an effect on the growth plates of long bones. Concentrations of IGF-1, which may play a role in skeletal growth, are low in the serum of growth-hormone-deficient children but increase during treatment with Humatrope. Elevations in mean serum alkaline phosphatase concentrations are also seen. 2. **Cell Growth**: It has been shown that there are fewer skeletal muscle cells in short-statured children who lack endogenous growth hormone as compared with normal children. Treatment with human growth hormone of pituitary origin results in an increase in both the number and size of muscle cells.

**B. Protein Metabolism**—Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows the initiation of therapy with human growth hormone of pituitary origin. Treatment with Humatrope results in a similar decrease in serum urea nitrogen.

**C. Carbohydrate Metabolism**—Children with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with Humatrope. Large doses of human growth hormone may impair glucose tolerance.

**D. Lipid Metabolism**—In growth-hormone-deficient patients, administration of human growth hormone of pituitary origin has resulted in lipid mobilization, reduction in body fat stores, and increased plasma fatty acids.

**E. Mineral Metabolism**—Retention of sodium, potassium, and phosphorus is induced by human growth hormone of pituitary origin. Serum concentrations of inorganic phosphate increased in patients with growth hormone deficiency after therapy with Humatrope or human growth hormone of pituitary origin. Serum calcium is not significantly altered in patients treated with either human growth hormone of pituitary origin or Humatrope.

#### INDICATION AND USAGE

Humatrope® (Somatropin, rDNA Origin, for Injection) is indicated only for the long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

#### CONTRAINDICATIONS

Humatrope® (Somatropin, rDNA Origin, for Injection) should not be used in subjects with closed epiphyses.

Humatrope should not be used when there is any evidence of activity of a tumor. Intracranial lesions must be inactive and antitumor therapy complete prior to the institution of therapy. Humatrope should be discontinued if there is evidence of tumor growth.

Humatrope should not be reconstituted with the supplied Diluent for Humatrope by patients with a known sensitivity to either m-cresol or glycerin.

#### WARNING

If sensitivity to the diluent should occur, the vials may be reconstituted with Sterile Water for Injection, USP. When Humatrope® (Somatropin, rDNA Origin, for Injection) is reconstituted in this manner, (1) use only 1 reconstituted dose per vial, (2) refrigerate the solution (36° to 46°F [2° to 8°C]) if it is not used immediately after reconstitution, (3) use the reconstituted dose within 24 hours, and (4) discard the unused portion.

#### PRECAUTIONS

Therapy with Humatrope® (Somatropin, rDNA Origin, for Injection) should be directed by physicians who are experienced in the diagnosis and management of patients with growth hormone deficiency.

Patients with growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process. Because human growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance.

Excessive glucocorticoid therapy will inhibit the growth promoting effect of human growth hormone. Patients with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth.

Hypothyroidism may develop during treatment with human growth hormone, and inadequate treatment of hypothyroidism may prevent optimal response to human growth hormone. Therefore, patients should have periodic thyroid function tests and be treated with thyroid hormone when indicated.

Patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital epiphyses more frequently. Any child with the onset of a limp during growth hormone therapy should be evaluated.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products. Symptoms usually occurred within the first eight (8) weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or a reduction of the growth hormone dose. Funduscopic examination of patients is recommended at the initiation and periodically during the course of growth hormone therapy.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term animal studies for carcinogenicity and impairment of fertility with this human growth hormone (Humatrope) have not been performed. There has been no evidence to date of Humatrope-induced mutagenicity.

**Pregnancy—Pregnancy Category C**—Animal reproduction studies have not been conducted with Humatrope. It is not known whether Humatrope can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Humatrope should be given to a pregnant woman only if clearly needed.

**Nursing Mothers**—There have been no studies conducted with Humatrope in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Humatrope is administered to a nursing woman.

#### ADVERSE REACTIONS

Approximately 2% of 481 naive and previously treated clinical trial patients treated with Humatrope® (Somatropin, rDNA Origin, for Injection, Lilly) have developed antibodies to growth hormone, as demonstrated by a binding capacity determination threshold  $\geq 0.02 \mu\text{g/mL}$ . Nevertheless, even these patients experienced increases in linear growth and other salutary effects of Humatrope and did not experience any unusual adverse events. Although growth-limiting antibodies have been observed with other growth hormone preparations (including products of pituitary origin), antibodies in patients treated with Humatrope have not limited growth. The long-term implications of antibody development are uncertain at this time.

Of the 232 naive and previously treated clinical trial patients receiving Humatrope for 6 months or more, 4.7% had serum binding of radiolabeled growth hormone in excess of twice the binding observed in control sera when the serum samples were assayed at a tenfold dilution. Among these patients were 160 naive patients, of whom 6.9% had positive serum binding. In comparison, 74.5% of 106 naive patients treated for 6 months or more with somatrem (produced by Lilly) in a similar clinical trial had serum binding of radiolabeled growth hormone of at least twice the binding observed in control sera.

In addition to an evaluation of compliance with the treatment program and of thyroid status, testing for antibodies to human growth hormone should be carried out in any patient who fails to respond to therapy.

In clinical studies in which high doses of Humatrope were administered to healthy adult volunteers, the following events occurred infrequently: headache, localized muscle pain, weakness, mild hyperglycemia, and glucosuria. In studies with growth-hormone-deficient children, injection site pain was reported infrequently. A mild and transient edema, which appeared in 2.5% of patients, was observed early during the course of treatment.

Leukemia has been reported in a small number of children who have been treated with growth hormone, including

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\* Identical symbol. This product information was prepared in June 1995. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46286, 800-545-5979.